

# THE LANCET Infectious Diseases

## Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed.  
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## **ONLINE APPENDIX**

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### **Title:**

***Middle East Respiratory Syndrome Coronavirus: Risk Factors and Determinants of Primary, Household, and Nosocomial Transmission***

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**Appendix 1a:**

**Selected publications of dromedary camels as the source of MERS-CoV infection in humans**

<b>Authors</b>	<b>Main findings</b>
Dudas G, et al. 2018	Based on existing MERS-CoV sequence data to examine the phylo-dynamics in camels and humans with structured coalescent model, Dudas et al show that long-term evolution of MERS-CoV occurs exclusively in camels while humans serve as a transient and terminal host ultimately. In addition, the study has shown that human outbreaks in the Arabian Peninsula have been driven by seasonally varying zoonotic transfer of viruses from camels.
Kasem S, et al. 2017	An investigation of animal herds associated with MERS-infected patients in Saudi Arabia, during 2014-2016. Seventy-five dromedary camels positive for MERS-CoV RNA; the virus was not detected in sheep, goats, and cattle. MERS-CoV RNA from infected camels was not detected beyond 2 weeks after the first positive result was detected in nasal swabs obtained from infected camels. Anti-MERS ELISA assays showed that 70.9% of camels related to human cases had antibodies to MERS-CoV. The full genome sequences of the ten MERS-CoV camel isolates were identical to their corresponding patients and were grouped together within the larger MERS-CoV sequences cluster for human and camel isolates reported from the Arabian Peninsula.
Lau SK, et al. 2017	219 camel and human MERS-CoV genome sequences available in GenBank were analyzed. Phylogenetic analysis showed that 5 and 214 strains belong to clade A and B, respectively, with clade A further divided into lineage A1 (3 human strains) and lineage A2 (2 camel strains), and clade B divided into B1 to B6 (each containing both human and camel strains). Recombination analysis showed potential recombination events in five strains from dromedaries in Saudi Arabia, with recombination between lineage B5 and B3 in four strains, and between lineage B3 and B4 in one strain. The spike protein showed the highest number of amino acid substitutions, especially between A2 and other lineages, and contained positively selected codons. Notably, codon 1020 was positively selected among B and B5 strains, and can distinguish between clade A (Q1020) and B (R1020/H1020) strains, suggesting that this residue may play a role in the evolution of S protein during divergence of different lineages. The time of the most recent common ancestor of all MERS-CoV was dated to approximately 2010.
Muhairi SA, et al. 2016	Nasal swabs from 1113 dromedary camels (39 farms) and 34 sheep (1 farm) and sputum samples from 2 MERS-CoV infected camel farm owners and 1 MERS-CoV-infected sheep farm owner were collected in Abu Dhabi. Samples from camels and humans underwent real-time quantitative RT-PCR screening to detect MERS-CoV. In addition, sequencing and phylogenetic analysis of partially characterize MERS- CoV genome fragments obtained from camels were performed. Among the 40 farms, 6 camel farms were positive for MERS-CoV; the virus was not detected in the single sheep farm. The maximum duration of viral shedding from infected camels was 2 weeks after the first positive test result as detected in nasal swabs and in rectal swabs obtained from infected calves. Three partial camel sequences characterized in this study (ORF 1a and 1ab, Spike1, Spike2, and ORF4b) together with the corresponding regions of previously reported MERS-CoV sequence obtained from one farm owner were clustering together within the larger MERS-CoV sequences cluster containing human and camel isolates reported for the Arabian Peninsula.

Farag EA, et al. 2015	A high proportion of camels presenting for slaughter in Qatar showed evidence for nasal MERS-CoV shedding (62/105). Sequence analysis showed the circulation of at least five different virus strains at these premises, suggesting that this location is a driver of MERS-CoV circulation and a high-risk area for human exposure. No correlation between RNA loads and levels of neutralizing antibodies was observed, suggesting limited immune protection and potential for reinfection despite previous exposure.
Reuskien CB et al, 2015	The investigators determined the presence of neutralizing antibodies to MERS-CoV in persons in Qatar with and without dromedary contact in 2013-2014. Antibodies were only detected in those with contact, suggesting dromedary exposure as a risk factor for infection. The study also showed evidence for substantial underestimation of the infection in populations at risk in Qatar.
Haagmans BL et al. 2014	Samples taken from 14 camels on October 17th, 2013 in an outbreak investigation at a farm in Qatar. MERS-CoV detected in nose swabs from 3 camels by three independent RT-PCRs and sequencing. The nucleotide sequence of an ORF1a fragment (940 nucleotides) and a 4.2 kb concentrated fragment were very similar to the MERS-CoV from two human cases on the same farm and a MERS-CoV isolate from Hafr-Al-Batin. Eight additional camel nose swabs were positive on one or more RT-PCRs, but could not be confirmed by sequencing. All camels had MERS-CoV spike-binding antibodies that correlated well with the presence of neutralising antibodies to MERS-CoV.

## References:

Dudas G, Carvalho LM, Rambaut A, Bedford T. MERS-CoV spillover at the camel-human interface. *eLife* 2018;7:e31257 doi:10.7554/eLife.31257

Kasem S, Qasim I, Al-Hufofi A, et al. Cross-sectional study of MERS-CoV-specific RNA and antibodies in animals that have had contact with MERS patients in Saudi Arabia. *J Infect Public Health*. 2017 Oct 6. pii: S1876-0341(17)30257-5.

Lau SK, Wong AC, Lau TC, Woo PC. Molecular Evolution of MERS Coronavirus: Dromedaries as a Recent Intermediate Host or Long-Time Animal Reservoir? *Int J Mol Sci*. 2017 Oct 16;18(10). pii: E2138. doi: 10.3390/ijms18102138.

Muhairi SA, Hosani FA, Eltahir YM, et al. Epidemiological investigation of Middle East respiratory syndrome coronavirus in dromedary camel farms linked with human infection in Abu Dhabi Emirate, United Arab Emirates. *Virus Genes*. 2016;52(6):848-854.

Farag EA, Reusken CB, Haagmans BL, et al. High proportion of MERS-CoV shedding dromedaries at slaughterhouse with a potential epidemiological link to human cases, Qatar 2014. *Infect Ecol Epidemiol*. 2015;5:28305.

Reusken CB, Farag EA, Haagmans BL, et al. Occupational Exposure to Dromedaries and Risk for MERS-CoV Infection, Qatar, 2013-2014. *Emerg Infect Dis*. 2015;21(8):1422-1425.

Haagmans BL, Al Dhahiry SH, Reusken CB, et al. Middle East respiratory syndrome coronavirus in dromedary camels: an outbreak investigation. *Lancet Infect Dis*. 2014;14(2):140-145

### Appendix 1b:

#### Additional information: Situation update guidelines and infection control recommendations on MERS-CoV by global public health bodies

WHO	<p><b>MERS-CoV Daily updates, facts and figures</b>  <a href="http://www.who.int/emergencies/mers-cov/en/">http://www.who.int/emergencies/mers-cov/en/</a></p> <p><b>MERS-CoV factsheet</b>  <a href="http://www.who.int/mediacentre/factsheets/mers-cov/en/">http://www.who.int/mediacentre/factsheets/mers-cov/en/</a></p> <p><b>MERS-CoV: infection control for possible or confirmed cases</b>  <a href="http://www.who.int/csr/disease/coronavirus_infections/ipc-mers-cov/en/">http://www.who.int/csr/disease/coronavirus_infections/ipc-mers-cov/en/</a></p> <p><b>Travel advice for pilgrims</b>  <a href="http://www.who.int/ith/updates/20170601/en/">http://www.who.int/ith/updates/20170601/en/</a></p> <p><b>Management of asymptomatic persons who are RTPCR positive for MERS-CoV. Interim Guidance. Updated 3 Jan 2018.</b>  <a href="http://apps.who.int/iris/bitstream/10665/180973/1/WHO_MERS_IPC_15.2_eng.pdf?ua=1&amp;ua=1">http://apps.who.int/iris/bitstream/10665/180973/1/WHO_MERS_IPC_15.2_eng.pdf?ua=1&amp;ua=1</a></p>
FAO	<p><b>MERS-CoV situation update</b>  <a href="http://www.fao.org/ag/againfo/programmes/en/empres/mers/situation_update.html">http://www.fao.org/ag/againfo/programmes/en/empres/mers/situation_update.html</a></p>
US-CDC	<p><b>MERS-CoV- prevention and treatment</b>  <a href="https://www.cdc.gov/coronavirus/mers/about/prevention.html">https://www.cdc.gov/coronavirus/mers/about/prevention.html</a></p> <p><b>Preventing MERS-CoV from Spreading to Others in Homes and Communities</b>  <a href="https://www.cdc.gov/coronavirus/mers/hcp/home-care-patient.html">https://www.cdc.gov/coronavirus/mers/hcp/home-care-patient.html</a>  <a href="https://www.cdc.gov/coronavirus/mers/risk.html">https://www.cdc.gov/coronavirus/mers/risk.html</a></p> <p><b>People Who May Be at Increased Risk for MERS</b>  <a href="https://www.cdc.gov/coronavirus/mers/infection-prevention-control.html">https://www.cdc.gov/coronavirus/mers/infection-prevention-control.html</a></p>
UK-PHE	<p><b>Interim Infection Prevention and Control Recommendations for Hospitalized Patients with Middle East Respiratory Syndrome Coronavirus (MERS-CoV)</b> <a href="https://www.gov.uk/government/publications/merscov-infection-control-for-possible-or-confirmed-cases">https://www.gov.uk/government/publications/merscov-infection-control-for-possible-or-confirmed-cases</a></p> <p><b>MERS-CoV: advice for travellers returning from the Middle East</b>  <a href="https://www.gov.uk/government/publications/mers-cov-infographics-for-travellers-from-the-middle-east">https://www.gov.uk/government/publications/mers-cov-infographics-for-travellers-from-the-middle-east</a></p>
Saudi Arabia MoH	<p><b>FAQs coronavirus (MERS-CoV)</b>  <a href="https://www.moh.gov.sa/en/CCC/FAQs/Corona/Pages/default.aspx">https://www.moh.gov.sa/en/CCC/FAQs/Corona/Pages/default.aspx</a></p> <p><b>Infection prevention and control guidelines for the Middle East respiratory Syndrome Coronavirus (MERS-CoV) – Moh, Command and Control Centre, 4<sup>th</sup> Edition January 2017.</b>  <a href="https://www.moh.gov.sa/endepts/Infection/Documents/Guidelines-for-MERS-CoV.PDF">https://www.moh.gov.sa/endepts/Infection/Documents/Guidelines-for-MERS-CoV.PDF</a></p> <p><b>Middle East respiratory Syndrome Coronavirus; Guidelines for health care professionals. April, 2018 -v. 5.0 pdf. Saudi Arabia Ministry of health, Command and Control Centre.</b></p> <p><b>MERS-CoV Health guidelines</b>  <a href="https://www.moh.gov.sa/en/CCC/InformationCenter/Pages/default.aspx">https://www.moh.gov.sa/en/CCC/InformationCenter/Pages/default.aspx</a></p>
ECDC	<p><b>ECDC Middle East respiratory Syndrome Coronavirus (MERS-CoV)</b>  <a href="https://ecdc.europa.eu/en/middle-east-respiratory-syndrome-coronavirus">https://ecdc.europa.eu/en/middle-east-respiratory-syndrome-coronavirus</a>  <a href="https://ecdc.europa.eu/en/middle-east-respiratory-syndrome-coronavirus/factsheet">https://ecdc.europa.eu/en/middle-east-respiratory-syndrome-coronavirus/factsheet</a></p>